Authors' Response to:

Review of Paulozzi, LJ, et al, "Lack of Evidence that Prescription Drug Monitoring Programs Decrease Deaths from Opioid Overdose"

By Lesley Curtis

Are the study objectives clearly stated and appropriate? (Yes, No, Unsure) Why?
Yes, study objectives are clear although I would advise against using causal language in the statement of the objective. Given the study design and available data, it would be more accurately stated as, "To quantify the relation (or association between) PDMPs and rates of death..."

Response: We removed causal language and now refer to "associations with" or "relations to" the outcomes in the abstract, Introduction, and Discussion.

Is the overall study design appropriate for the study objectives? (Yes, No, Unsure) Why?
Yes

Are the methods and analysis plan appropriate for the study objectives? (Yes, No, Unsure) Why?
Generally, yes. I agree with the previous reviewer that the author will likely need to explain the schedule of controlled substances. In addition, the definition of "proactive" PDMPs seems subjective. A better rationale for the definition should be provided.

Response: We added more information on the top of page 7 saying that there are 4 schedules for prescription drugs, II is the most regulated, and III has fewer restrictions on refills, documentation, etc. The definition for "proactive" is the one generally accepted by state PDMPs. However, no official definition has been published.

Were the data analyzed in such a way to address the objectives of the study appropriately? (Yes, No, Unsure) Why?
Generally, yes. What does the term "geographically lagged" mean? Depending on the target journal, this paragraph on p.8 may need to be expanded and written more clearly. Autocorrelation, for example, is not a term typically used in medical journals.

Response: We've revised the text on the bottom of page 8 to explain these terms.

Are the study results presented and interpreted appropriately and completely? (Yes, No, Unsure) Why?
Yes

Are the study conclusions, policy implications, and recommendations appropriate and complete? (Yes, No, Unsure) Why?

Is there reason to expect that PDMPs would reduce drug overdose deaths? The link between PDMPs and drug abuse/addiction seems clearer. Couldn't a patient overdose on a single prescription of many of the drugs being examined? It would be helpful to make the link between PDMPs and overdose more clearly for the reader.

Response: A person could overdose on a single pill in some cases, but the literature suggests that few patients overdose fatally without a prior history of substance abuse (Hall 2007, Hempstead 2006) and without consuming substantially higher daily doses than the average patient (Franklin,AJIM, 2005). We believe PDMPs in theory reduce substance abuse and that in turn reduces overdoses, Also, old studies, some of which are cited in the paper, have shown that PDMPs using paper forms reduced both the amounts of drug prescribed and emergency department overdose visits.

We have tried to make this connection more explicit by adding a sentence to the Introduction stating that persons dying of prescription drug overdoses generally have a history of abusing prescription drugs, often without a prescription.

Additional comments tracked in the text are addressed below:

Page 3 (Abstract): *The comparison was clarified. Variability in drug overdose mortality in 2005, for example, was large. The range was from 1.0 to 17.5/100,000. The middle tertile range was from 7.5 to 9.9. We added the overall range as the first sentence of the Results section.*

Page 4 (Methods): *The N for the study was 51 x 7 years or 357.We added this later in the Methods on page 7.*

Page 7: What are the total MME and MME by drug type?:

Response: Total MME by year is given in Figure 4. The annual totals for hydrocodone and the Schedule II drugs are shown in Figure 6. We didn't anticipate any association of individual opioids with drug overdose rates that would confound (disguise) an overall association between PDMPs and those rates. So we did not look at quantities of individual opioids as covariates.

Page 9: "There needs to be a table that summarizes the key variables of interest in the study sample. Graphs are not sufficient."
Response: It wouldn't be practical to show values for each state per year. The Figures show the means per year for the various groups. However, we have added a table showing the mean values for each outcome variable by categories of states, eg, those with PDMPs, proactive states, etc.

Page 11: "It would be helpful to describe the variation in the implementation of PDMPs earlier. "
Response: We put a sentence about the form variation in the Introduction.

Page 12: Why weren't special forms among the a priori hypotheses?
Response: We didn't have it as a hypothesis at the outset of the study. We only realized there was previous literature on the subject of paper forms after noting the finding for the states with paper forms and trying to explain it.

Page 13: Comment re studying states before and after PDMP implementation.
Response: We added an explanation for why this before-after study design was not possible to page 14. Basically only six states started data collection during the interval during which we had valid opioid mortality data and ARCOS drug distribution data. In response to this comment, we conducted a before-after analysis of just those six states. The results were consistent with the results for all 50 states in the paper, i.e., no significant change in the outcomes after starting a PDMP. We have attached this special additional analysis in an Appendix.

Appendix
OCTOBER 13, 2009 (rev. October 20)
NOTE TO "STUDY A" TEAM / FOR THE RECORD
FROM ED KILBOURNE

RE: "DIFFERENCE OF DIFFERENCES" ANALYSIS

SUMMARY

I've now completed a focused and much more extensive "Difference of Differences" analysis on the "Study A" data. The results show no statistically significant[1] differences of differences for any of the outcomes.

RATIONALE

The reason for investigating this matter in further depth is the possibility that our regression analysis of differenced values could have "diluted" an effect that would be more clearly visible in a study limited to the states that changed status (from non-PDMP to PDMP) during the study period. (There were no states changing from PDMP to non-PDMP status.)

INTRODUCTION

There were six states that contributed both PDMP and non-PDMP state-years to the study. They (and their PDMP starting years) are shown in Table 1.

Table 1.

STATE	START
PA	2002
VA	2003
ME	2004
WY	2004
MS	2005
NM	2005

For the descriptive data that follow, I normalized the years of program start by subtracting the study starting year less one from each of the program years for each state. Thus Year=1 for PA represents 2002, but Year=1 for WY indicates 2004 (i.e., events occurring two years later). Year=0 means the year prior to implementation, Year= -1 means two years prior to implementation, Year= -2 means three years prior, and so forth.

DRUG OVERDOSE MORTALITY

The rates of drug overdose mortality (deaths per 100,000 persons) for the six states are shown in Table 2.

[1] Differences discussed herein are considered statistically significant where $P \leq 0.05$.

Table 2.

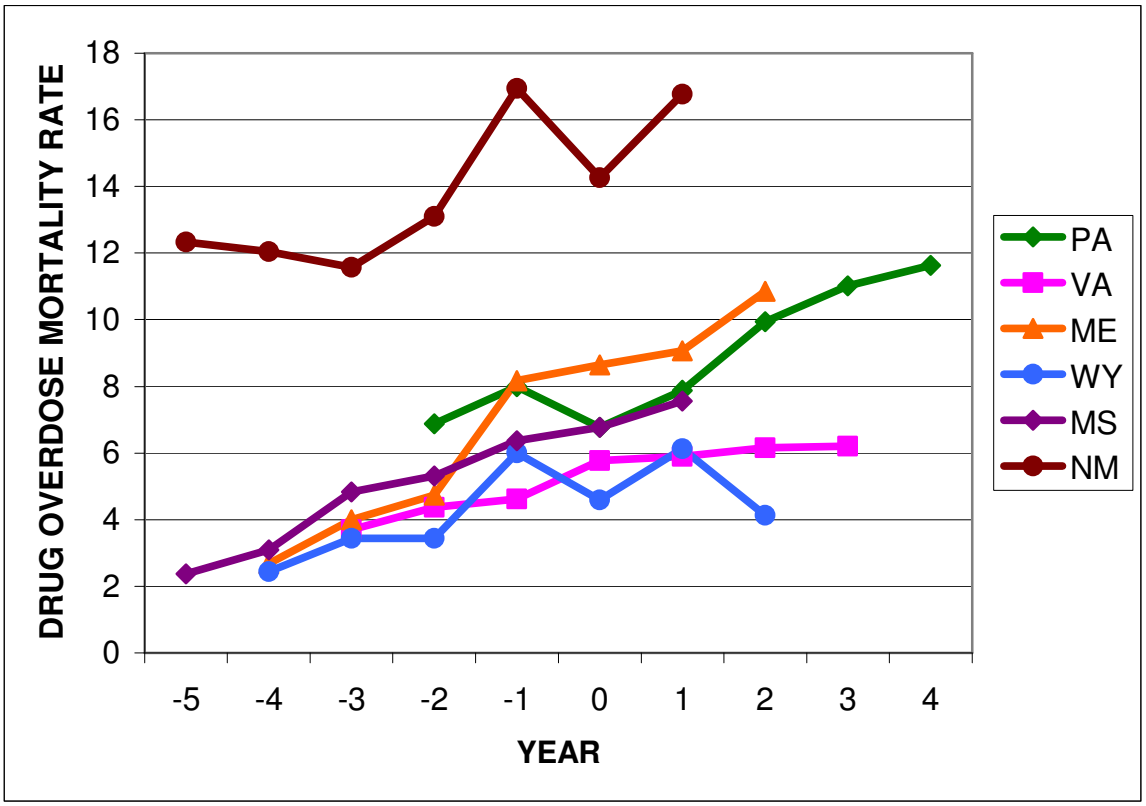
YEAR	PA	VA	ME	WY	MS	NM
-5					2.37	12.33
-4			2.68	2.44	3.09	12.04
-3		3.70	4.00	3.44	4.83	11.57
-2	6.88	4.37	4.74	3.44	5.31	13.10
-1	8.00	4.62	8.17	6.01	6.37	16.94
0	6.78	5.78	8.64	4.59	6.78	14.26
1	7.88	5.90	9.06	6.13	7.56	16.77
2	9.94	6.16	10.85	4.13		
3	11.01	6.21				
4	11.63					

= No PDMP

= PDMP

If one graphs these rates for the six states over time, they appear as shown in Figure 1.

Figure 1.



The rates of drug overdose mortality in Table 2 and Figure 1 are in no way differenced. Note that they have a clear-cut upward trend.

Differenced values reflect the difference in a rate from the previous time period. A first-order year-to-year difference in a statistic is the statistic for one year after subtracting that same statistic for the previous year.

The first-order differences for the above rates appear as follows in Table 3.

Table 3.

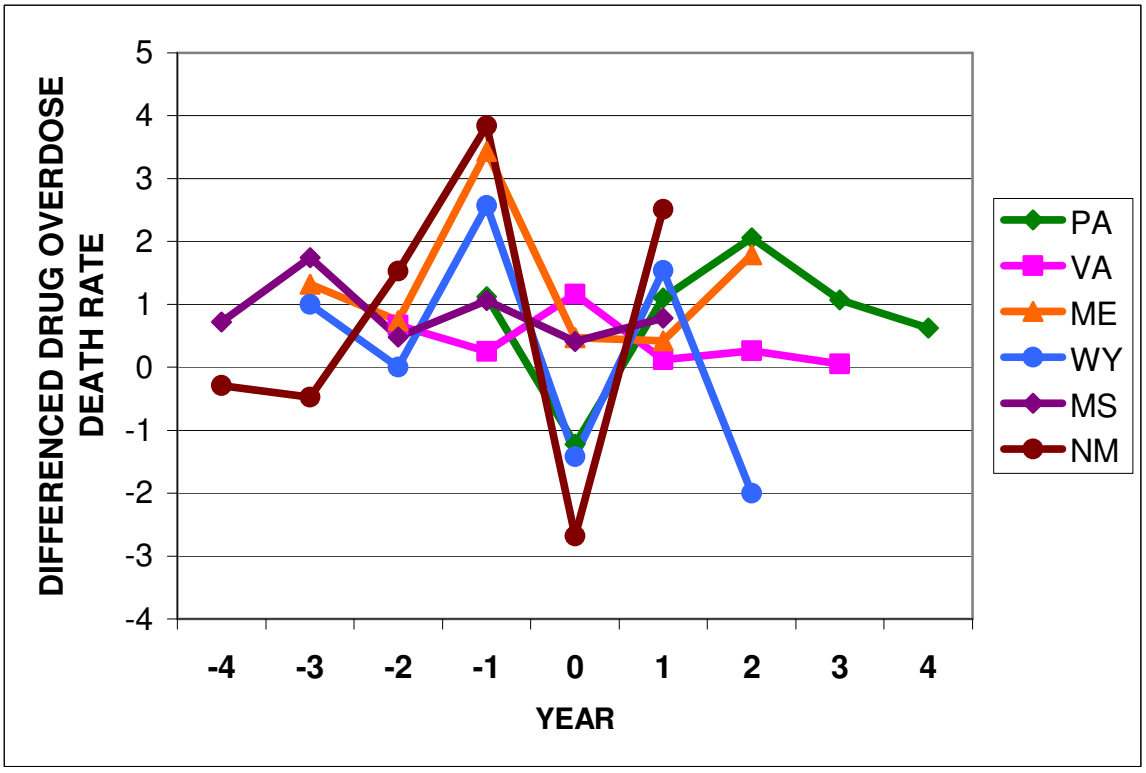
YEAR	PA	VA	ME	WY	MS	NM
-4					0.72	-0.29
-3			1.32	1.00	1.74	-0.47
-2		0.67	0.74	0.00	0.48	1.53
-1	1.12	0.25	3.43	2.57	1.06	3.84
0	-1.22	1.16	0.47	-1.42	0.41	-2.68
1	1.10	0.12	0.42	1.54	0.78	2.51
2	2.06	0.26	1.79	-2.00		
3	1.07	0.05				
4	0.62					

= No PDMP

= PDMP

A line graph of these values over time is shown as Figure 2.

Figure 2.



Differencing is analogous to taking the first derivative in the Calculus. Thus, the pronounced upward trend (analogous to a sloped straight line) is mitigated (analogous to conversion of a straight, sloped line to a horizontal line by taking the first derivative). The question remaining now is whether the year to year differences are lower when YEAR ≥ 1.

But before we can pool data points, one problem remains. Even after differencing, the statistics from the six states are by no means the same with regard to their means and variances. Between-state differences in their mean values could possibly decrease the sensitivity of the difference of differences analysis by amplifying the variance of data points in the two groups: "before" and "after" the intervention (the PDMP).

Between-state differences in variance are also potentially problematic. States with larger variances will tend to have "influential points" (much higher and much lower) after differencing and may have a disproportionate effect on any summary measures, potentially biasing the analysis in unpredictable ways. As an example, from observation of the above graph, one notes that the variance (over time) of the differenced rates from New Mexico seems to be substantially greater than that of most of the other states.

To deal with these problems, one convert the data into "standard scores" to equalize means and standard deviations. Note that making the overall means for the states equal will tend to amplify (not mask) a difference between "before" and "after." Standardizing the means does this by eliminating between state differences that are irrelevant to the "before" and "after" conditions.

Conversion of data to "Z-scores" normalizes both mean and variance. A Z-scored variable has a mean of zero and a standard deviation of one. The formula for standardizing data in this way is given as Equation 1.

Equation 1.

$$Z = \frac{x - \mu}{\sigma}$$

where x is the value for a particular state and year, μ is the mean for the state, and σ is the standard deviation for the state. (There are nuances of standardized scoring that depend on whether one is dealing with population statistics or population estimates, but I omit them here for simplicity.) The standardized, differenced data for the drug overdose death outcome are shown in Table 4.

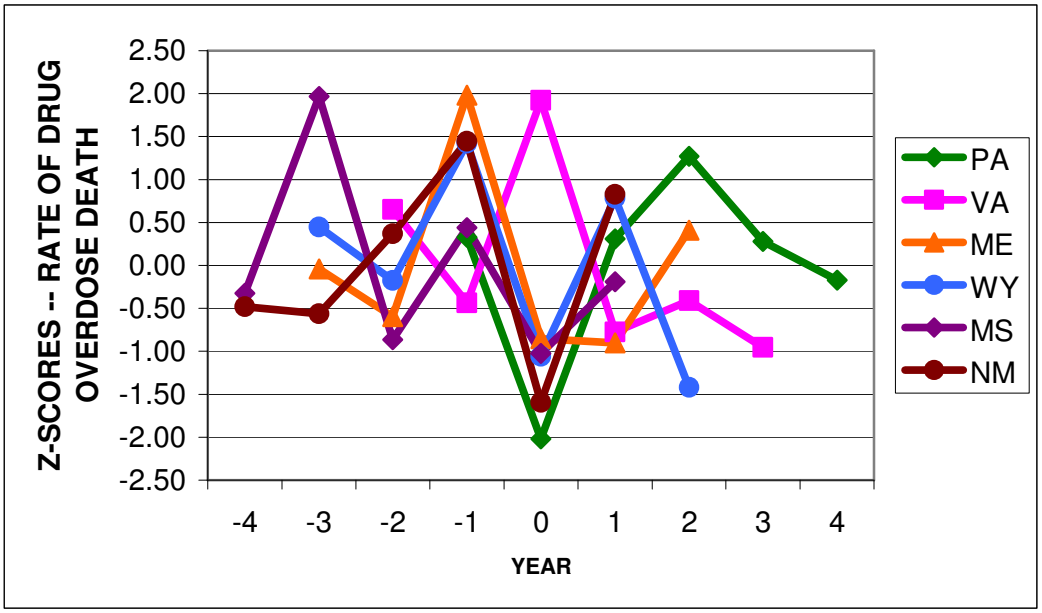
Table 4.

YEAR	PA	VA	ME	WY	MS	NM
-4					-0.33	-0.48
-3			-0.04	0.45	1.97	-0.56
-2		0.65	-0.60	-0.18	-0.87	0.37
-1	0.33	-0.44	1.98	1.42	0.44	1.45
0	-2.02	1.92	-0.85	-1.06	-1.02	-1.59
1	0.31	-0.77	-0.90	0.78	-0.19	0.83
2	1.27	-0.41	0.41	-1.42		
3	0.28	-0.96				
4	-0.17					

= No PDMP

= PDMP

The same numbers, displayed graphically are shown in Figure 3:



No particular difference is evident in Figure 3 at Year ≥ 1. However, for further assurance, we divide the data points (now differenced and standardized) into two groups: "Before" and "After." The statistics derived are as follows:

Table 5.

GROUP	N	MEAN	S.E.	DF	T	P
BEFORE	23	0.04	0.24	34	0.3175	0.7528
AFTER	13	-0.07	0.22			

There is a trend toward lesser year-to-year increases in drug overdose death rates in these 6 states. However, it is not nearly statistically significant at the 0.05 level.

OPIOID-RELATED MORTALITY

The parallel analyses for opioid-related mortality can be summarized in the following tables and figures:

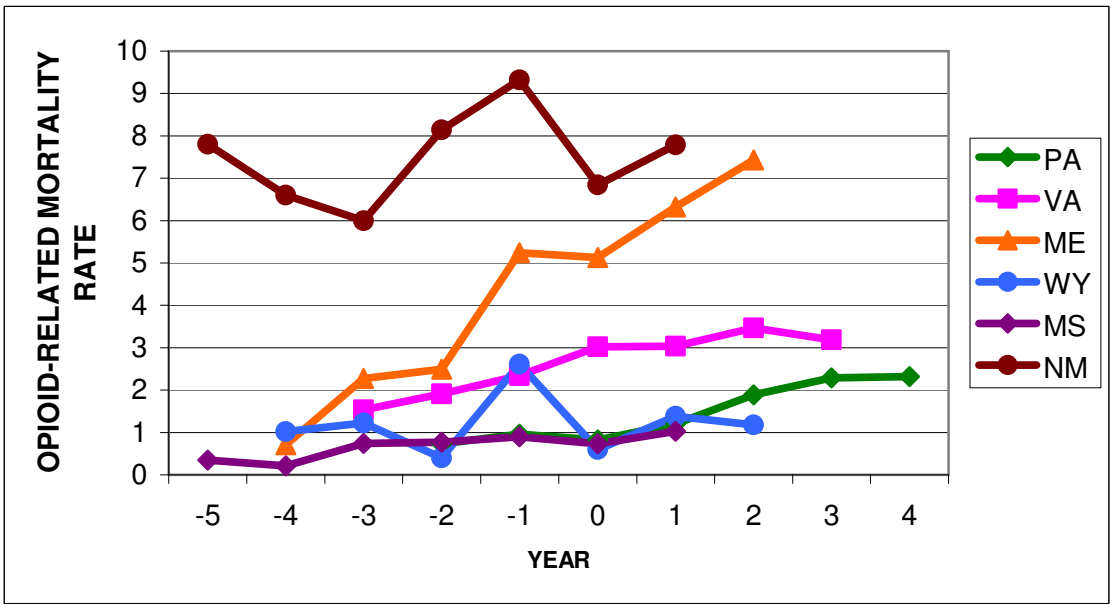
Table 6. Rate of opioid-related mortality by year relative to the starting year of the PDMP Program

YEAR	PA	VA	ME	WY	MS	NM
-5					0.35	7.80
-4			0.71	1.02	0.21	6.60
-3		1.53	2.27	1.22	0.74	6.00
-2	0.73	1.91	2.49	0.40	0.77	8.14
-1	0.96	2.34	5.24	2.61	0.90	9.32
0	0.82	3.02	5.13	0.60	0.73	6.84
1	1.20	3.04	6.32	1.38	1.03	7.79
2	1.89	3.47	7.43	1.18		
3	2.29	3.19				
4	2.32					

= No PDMP

= PDMP

Figure 4. Opioid-Related Mortality Rates by Year Relative to the Starting Year of the PDMP Program



Differenced values of opioid-related mortality rates by state are as follows in Table 7 and Figure 5:

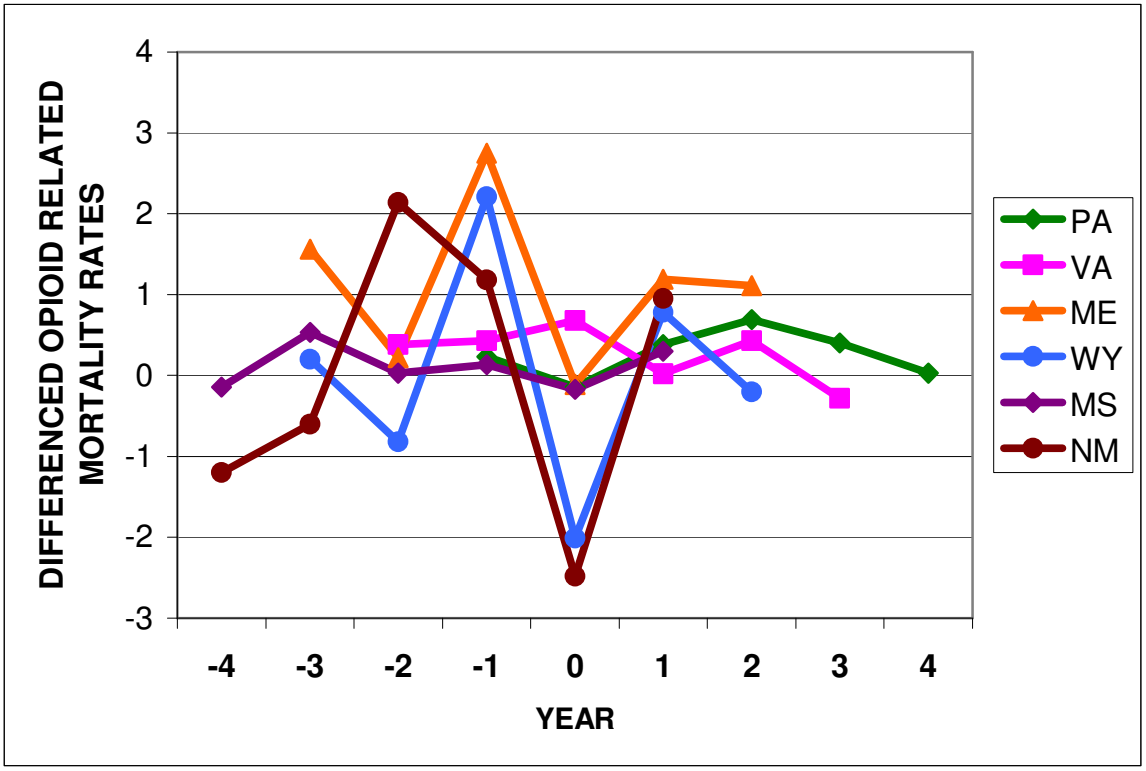
Table 7.

YEAR	PA	VA	ME	WY	MS	NM
-4					-0.14	-1.20
-3			1.56	0.20	0.53	-0.60
-2		0.38	0.22	-0.82	0.03	2.14
-1	0.23	0.43	2.75	2.21	0.13	1.18
0	-0.14	0.68	-0.11	-2.01	-0.17	-2.48
1	0.38	0.02	1.19	0.78	0.30	0.95
2	0.69	0.43	1.11	-0.20		
3	0.40	-0.28				
4	0.03					

= No PDMP

= PDMP

Figure 5.



The differenced rates of opioid-related mortality must be standardized, just as for the differenced drug overdose mortality rates:

Table 8. Standard (Z) scores for opioid-related mortality rates.

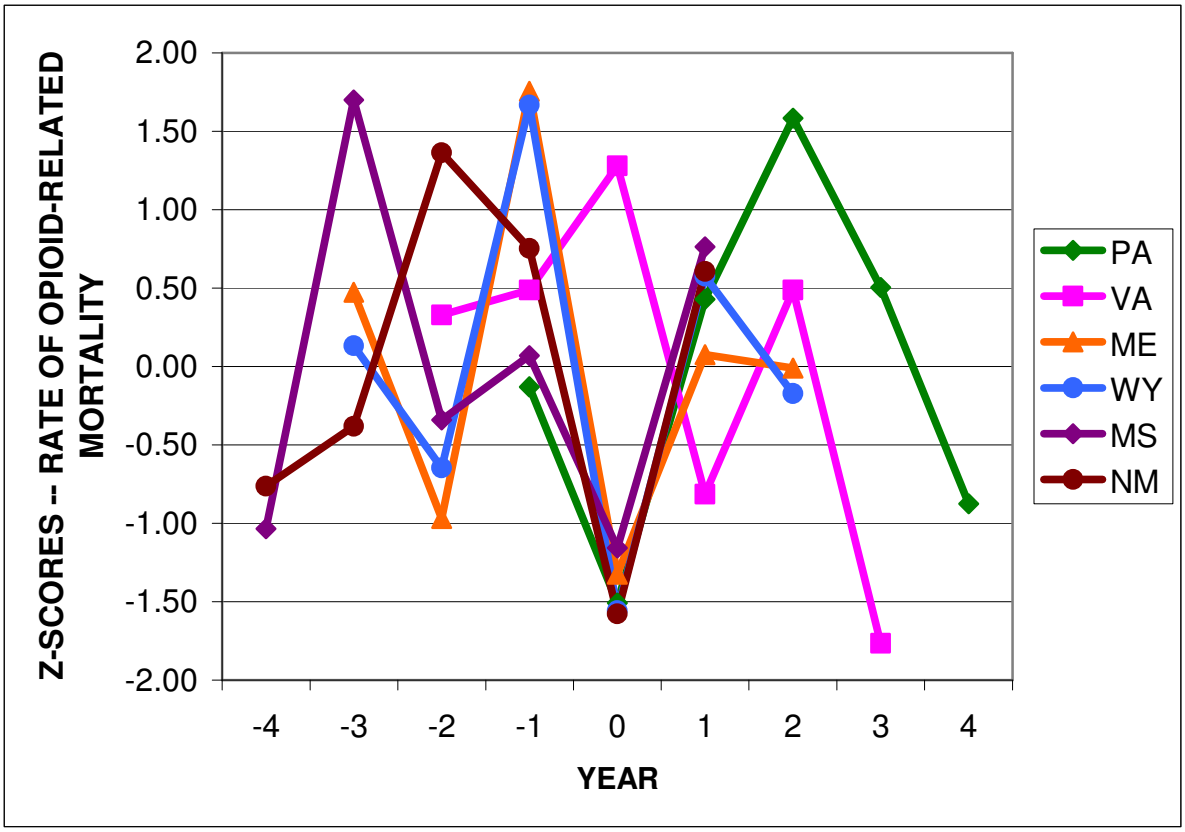
YEAR	PA	VA	ME	WY	MS	NM
-4					-1.03	-0.76
-3			0.47	0.13	1.70	-0.38
-2		0.33	-0.97	-0.65	-0.34	1.36
-1	-0.13	0.49	1.75	1.67	0.07	0.75
0	-1.51	1.28	-1.32	-1.56	-1.16	-1.58
1	0.43	-0.81	0.08	0.58	0.76	0.61
2	1.58	0.49	-0.01	-0.17		

= No PDMP

= PDMP

3	0.50	-1.77				
4	-0.88					

Figure 6. Standard (Z) scores for opioid-related mortality rates.



"Before and after" statistics for opioid drug overdoses can be calculated as before. They are shown in Table 9. As was the case for drug overdose mortality, there is no significant difference in opioid related mortality before and after implementing the PDMP. However, the opioid-related mortality analysis is slightly different in that the trend is toward a slightly worse outcome (that is, a greater year-to-year increase in rates of opioid-related mortality following institution of a PDMP.

Table 9.

GROUP	N	MEAN	S.E.	DF	T	P
BEFORE	23	-0.06	0.23	34	-0.4666	0.6438
AFTER	13	0.11	0.24			

TOTAL MORPHINE EQUIVALENTS PER PERSON-YEAR (TOTALMEQ)

Finally, The parallel analysis for the third and final outcome variable, the total morphine milligram equivalents per person per year (TOTALMEQ), can be summarized in the following tables and figures:

Table 10. Undifferenced values of TOTALMEQ by state and year relative to PDMP start date.

YEAR	PA	VA	ME	WY	MS	NM
-5					124	148
-4			223	136	169	194
-3		166	306	166	208	246
-2	199	219	389	222	264	287
-1	246	265	477	291	331	339
0	292	314	550	376	370	389
1	351	376	672	429	406	413
2	451	406	720	468		
3	487	417				
4	536					

= No PDMP

= PDMP

Figure 7. Undifferenced values for TOTALMEQ

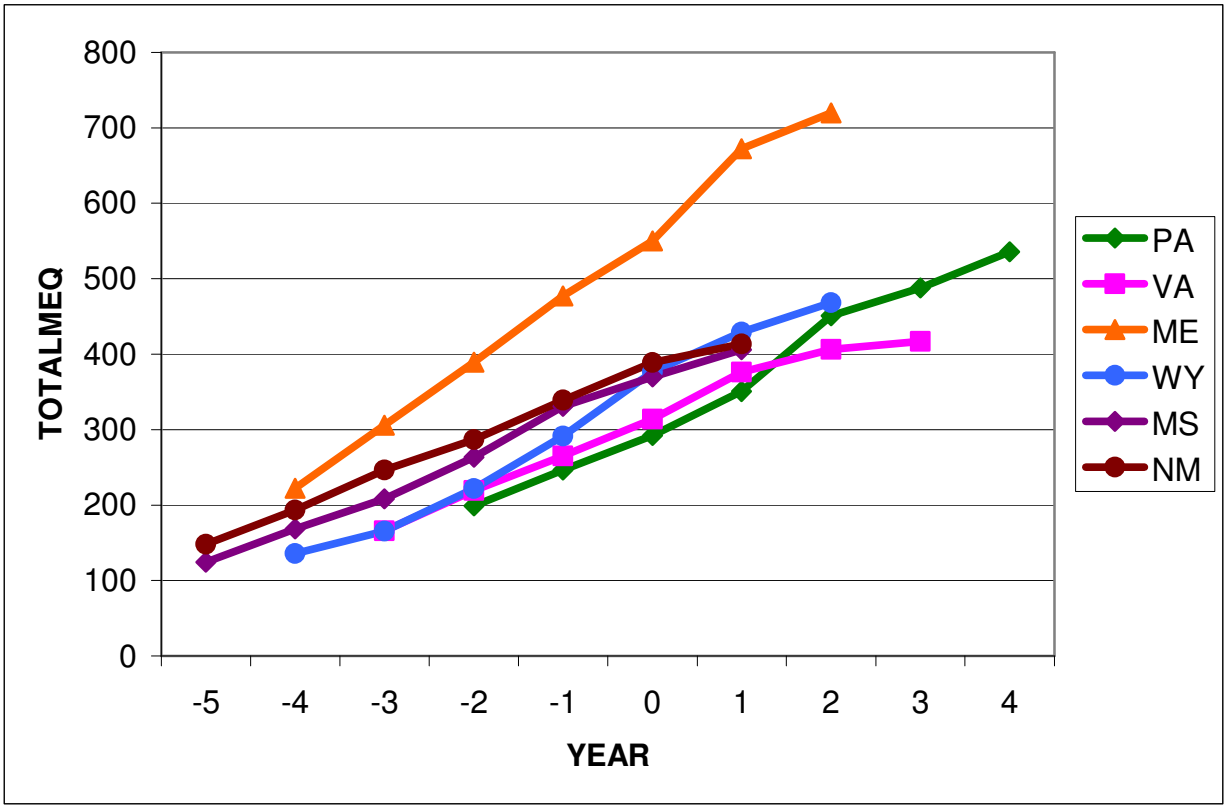


Table 11. Differenced values of TOTALMEQ by state and year relative to PDMP start date.

YEAR	PA	VA	ME	WY	MS	NM
-4					44	45
-3			84	30	40	53
-2		53	83	56	55	41
-1	47	46	88	69	68	52
0	46	49	73	85	39	50
1	58	62	123	53	36	24
2	100	30	48	39		
3	37	11				
4	48					

= No PDMP

= PDMP

Figure 8. Difference values of TOTALMEQ

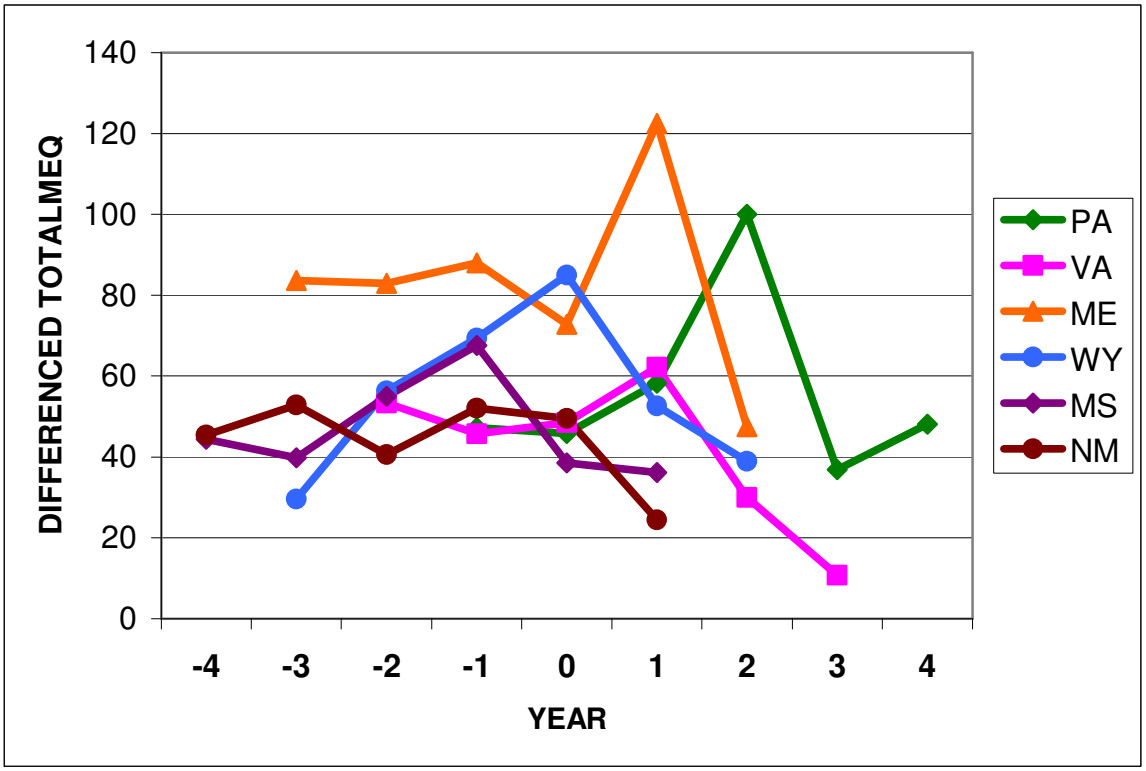


Table 12. Z-scored values of TOTALMEQ

YEAR	PA	VA	ME	WY	MS	NM
-4					-0.23	0.13
-3			0.03	-1.40	-0.65	0.89
-2		0.69	0.00	0.06	0.73	-0.36
-1	-0.43	0.24	0.23	0.77	1.87	0.81
0	-0.50	0.40	-0.45	1.62	-0.76	0.55
1	0.11	1.20	1.79	-0.15	-0.97	-2.02
2	2.13	-0.69	-1.60	-0.89		
3	-0.93	-1.84				
4	-0.38					

= No PDMP

= PDMP

Figure 9. Z-scored values of TOTALMEQ

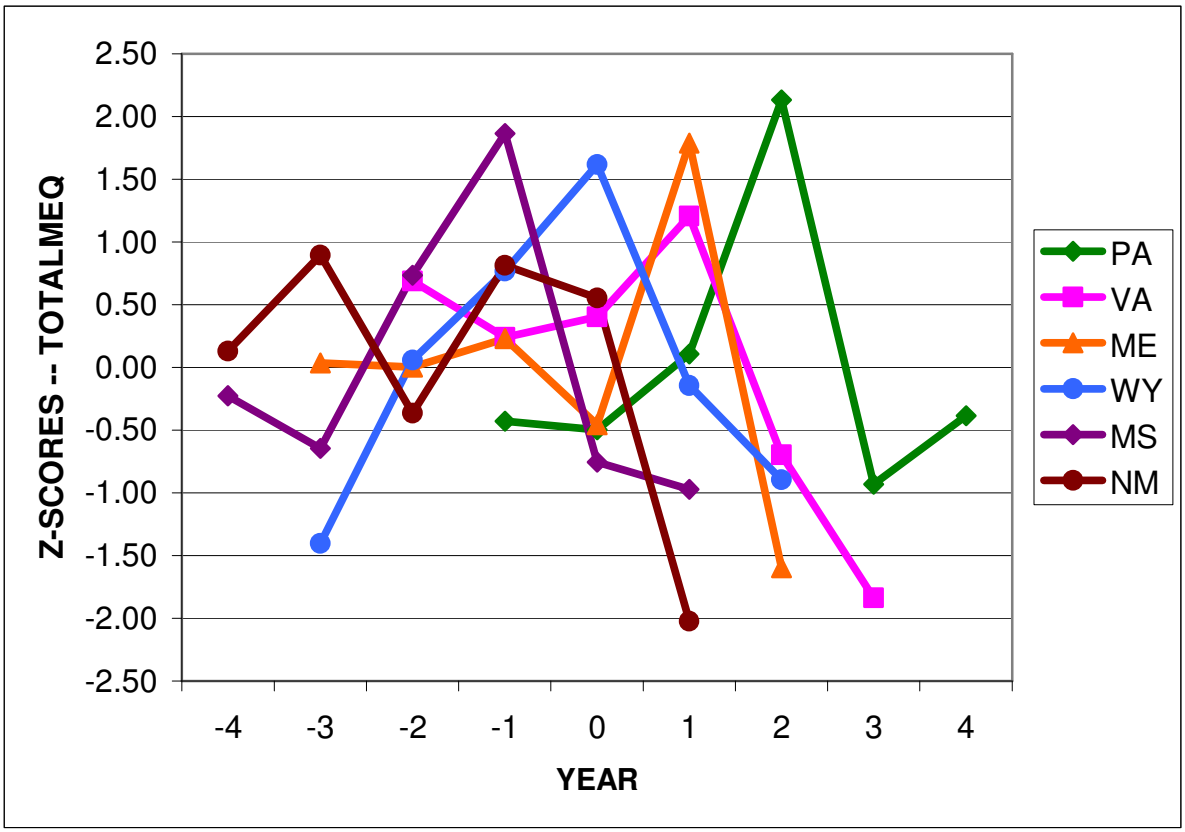


Table 13. "Before and after" comparison of TOTALMEQ

GROUP	N	MEAN	S.E.	DF	T	P
BEFORE	23	0.18	0.16	16.6	1.275	0.2199
AFTER	13	-0.33	0.37			

Thus the analysis of TOTALMEQ shows a trend toward lower year-to-year increases in total morphine equivalents per person in years occurring after institution of a PDMP. However, this trend is NOT statistically significant at the 0.05 level.

CONCLUSION

An analysis focused on the states that instituted PDMP's during the study period shows no statistically significant evidence of an impact of the programs on death rates (using either definition #1 (drug overdose) or definition #2 opioid-related mortality) nor does it show significantly lower year-to-year increases in opioid sales after states' initiation of PDMP's.

Thus, a focused difference-of-differences analysis has no impact on our findings.

- Ed Kilbourne.